A Multicenter observational Belgian study assessing the impact of newly started treatment on the QOL in patients suffering from myelodysplastic syndromes.

PROTOCOL

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Sponsor : UZA

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Principal Investigator	Date
Printed Name of Principal Investigator	

LOCAL INVESTIGATOR SIGNATURE PAGE

Local site name: _____

_____ _____

Signature of Local Investigator Date

_____

Printed Name of Local Investigator

By my signature, I agree to personally supervise the conduct of this study in my affiliation and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, the Declaration of Helsinki, ICH Good Clinical Practices guideline, the EU directive Good Clinical Practice (2001-20-EG), and local regulations governing the conduct of clinical studies.

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2 Protocol Summary

Study title

A multicenter observational Belgian study assessing the impact of newly started treatments on the QOL in patients suffering from myelodysplastic syndromes.

Background

A disease specific Quality of life (QOL) assessment gives a view on disease-related symptoms and psychological sequellae of patients suffering from a MDS(MDS). This QOL assessment tool, the QUALMS (Annex 1), was developed by Abel and colleagues at Dana-Farber institute and validated afterwards (1).

Another important aspect is the patients' perception of the disease. This can be measured using the brief illness perception questionnaire (B-IPQ)(Annex 2) (2).

Study type

An observational study conducted in different hematological centers in Belgium.

Study objectives

Primary objective:

To assess the impact of newly started treatments on the QOL of patients suffering from myelodysplastic syndromes.

Secondary objectives:

- To assess the impact of newly started therapy on disease perception in MDS patients
- To study the relation between disease perception and quality of life
- To examine which clinical and disease specific factors determine QOL in MDS patients
- Collect information on the transfusion threshold in Belgian hematological centers and evaluate the impact on quality of life.
- To evaluate whether changes in QOL are related to hematological respons.

Study design

- Newly diagnosed MDS patients who are about to start a treatment or previously diagnosed MDS patients who are starting with a new line of therapy.
- QOL assessment with the QUALMS.
- Disease perception measurement using the B-IPQ.
- Measurement at diagnosis/before start of therapy, at 4 weeks, 12 weeks, and at 24 weeks into treatment.

Study endpoints

Primary endpoint:

Change in QUALMS score at visit timepoints 4 – 12 – 24 weeks after the start of a new treatment.

Secondary endpoint:

- Change in B-IPQ score at visit timepoints 4 – 12 – 24 weeks after the start of a new treatment
- Association between B-IPQ and QUALMS score.
- Association between clinical and disease specific factors and QUALMS score
- Association between transfusion threshold and QUALMS score.
- Association between hematological response and QUALMS score

Summary of eligibility criteria

- Adult patients with a new diagnosis of MDS (according to WHO 2016 definitions (3) or known patients with MDS who are about to start a new treatment.
- Signed informed consent.
- Patients enrolled in an unblinded interventional therapeutic trial are eligible.

Exclusion criteria

- Patients with acute leukemia defined as >20% bone marrow blasts.
- Patients suffering from an overlap syndrome myelodysplastic/myeloproliferative disease.
- Patients in post allogeneic transplant setting.
- Patients enrolled in a blinded interventional therapeutic trial.
- Patients starting with multiple treatments under investigation at the same moment apart from intensive chemotherapy.
- Newly diagnosed patients who do not start with treatment.
- Patients who started a previous treatment less then 12 weeks ago apart from packed cell transfusion (up to 4 weeks allowed).
- Diagnosis of any previous or concomitant malignancy except when the patient successfully completed treatment (chemotherapy and/or surgery and/or radiotherapy) with curative intent for this malignancy at least 3 months prior to inclusion.
- Patients refusing to sign informed consent.

3 Investigators and study administrative structure

This is an investigator-initiated trial sponsored by UZA, which means that UZA holds all sponsor responsibilities unless it is explicitly stated in this protocol that a sponsor responsibility is delegated to another party.

Responsibility	**Name**	**Affiliation/Address**
Sponsor	UZA	
Principal Investigator	Z. Berneman	UZA
Co-investigators	B. Heyman	ZNA
	S. Meers	AZ KLINA
	D.A. Breems	ZNA
Statistician	UZA	
Registration	ZNA	
Trial management	ZNA	
Data management	ZNA	

4 Introduction and rationale

4.1 Myelodysplastic syndromes

Myelodysplastic syndromes refer to a heterogeneous group of clonal bone marrow disorders. They are characterized by malfunctioning of the bone marrow due to stem cells with aberrant morphology and maturation (dysmyelopoiesis). This is caused by cytogenetic abnormalities and molecular mutations. Bone marrow malfunctioning leads to one or more cytopenias in peripheral blood. Patients, most commonly in the aging population, frequently present with fatigue but recurrent infections or easy bleeding may occur in relation to the cytopenias that are found (4).

Depending on the findings in the bonemarrow and the genetic signature of the disease, patients are categorized in different risk groups to determine the risk for evolution to acute leukemia. The best implemented scoring system is the IPSS (International prognostic scoring system), assigning patients to the low, intermediate-1, intermediate-2 or high-risk category. The majority of patients present with lower-risk disease (low and intermediate-1) and have a survival of many years with supportive therapy only. Higher (intermediate-2 and high)-risk patients however demand more close attention and specific therapy to prevent evolution to acute leukemia. So far, the only curative option is allogeneic stem cell transplantation. Most patients however are not eligible for this intensive treatment (5). Apart from clinical trials, treatment options for this extensive group are limited. In lower risk diseases only supportive treatments can be offered with the exception of Del5q-syndrome in which lenalidomide is available. Only for higher risk patients, Vidaza® is reimbursed (6). Patients in need for treatment visit the hospital in a frequency that there therapy demands. Visits range between 15 minutes and whole day admissions depending on the treatment.

4.2 QOL assessment

Oxford dictionary defines the QOL as ‘the standard of health, comfort and happiness experienced by an individual or group.’ A broad range of life domains can influence this QOL so it is important to have attention for all of them when assessing quality of life. By assessing the quality of life, we can understand the general well-being of an individual or group. Based on this assessment, decisions can be made in general life, in a company but also in healthcare.

4.3 QOL assessment in MDS

To assess the QOL in the general population, different tools were developed in the past. Mostly they consist of questionnaires that try to cover all relevant topics that might have an influence on the quality of life.

If a subgroup of the population is approached, different topics become more relevant. For example, living above a supermarket at the age of 75 can have a totally different impact on QOL then at a younger age and working night shifts.
Fatigue as a result of anemia is the most frequent symptom of myelodysplastic syndromes. Assessment of QOL in the MDS population focused on this in the past. The FACT (functional assessment of cancer therapy) questionnaires for anemia (FACT-AN) and fatigue (FACT-Fatigue) were used to evaluate the efficacy of ESA (7). Higher risk diseases have been approached with focus on the malign aspect of the disease, using the EORTC C30 (8). However, since those assessments do not necessarily cover the subtleties of the disease, a specific questionnaire was developed. The use of this questionnaire gives us a specific assessment for disease-related symptoms and psychological sequellae of MDS patients (1). This specific questionnaire, the QUALMS will be used in this study to evaluate the QOL of patients suffering from MDS.

5 Study objectives

With growing sense of self-determination in Belgium, QOL becomes more relevant then it used to be. With this study, we aim to:
Primary objective:
assess the impact of newly started treatments on the QOL of patients suffering from myelodysplastic syndromes.
Secondary objectives:
- assess the impact of newly started therapy on disease perception in MDS patients.
- study the relation between disease perception and quality of life
- examine which clinical and disease specific factors determine QOL in MDS patients
- collect information on the transfusion threshold in Belgian hematological centers and evaluate the impact on quality of life.
- evaluate whether changes in QOL are related to hematological respons.

This study will not mutually compare the effect that different treatments have on QoL since the studied treatments will be installed at different stages of the disease and have different indications.

6 Study design

This study is an observational study conducted in different hematological centers in Belgium. The study will be conducted within the ‘MDS Working Group’ of the ‘Belgian Hematological Society’. This working group is attended by members of different academic and non-academic hematological centers. Centers who are not represented in the working group will be approached only if follow up of MDS patients is done by a certified hematologist.

The QOL of will be measured in patients who are newly diagnosed with MDS or known patients that are about to start a new therapy. Patients that do not start with a treatment can not participate.
All treatment discisions are made by the treating haematologist, this study will not interfere with this discions at any timepoint.

7 Study population

7.1 Eligibility for registration

All eligible patients must be registered before start of treatment and must meet all of the following eligibility criteria which will be checked at registration.

7.1.1 Inclusion criteria

- Newly diagnosed patients with myelodysplastic syndromes defined by WHO 2016 criteria that are about to start treatment.
- Patients with a known diagnosis of MDS, irrespective of IPSS and irrespective of time of diagnosis that are about to start a new therapy.
- Signed informed consent

7.1.2 Exclusion criteria

- Patients with acute leukemia defined as >20% bone marrow blasts.
- Patients suffering from a myelodysplastic/myeloproliferative overlap syndrome. In this case the disease has both dysplastic and proliferative features but cannot be properly categorized to either group. This category includes chronic myelomonocytic leukemia (CMML), juvenile myelomonocytic leukemia (JMML), atypial chronic myeloid leukemia (aCML) and myelodysplastic/myeloproliferative disease unclassifiable.
- Patients in post allogeneic transplant setting.
- Patients enrolled in a blinded interventional therapeutic trial.
- Patients starting with multiple MDS treatments at the same moment apart from intensive chemotherapy.
- Newly diagnosed patients who do not start with treatment.
- Patients who started a previous MDS related treatment less then 4 weeks ago.
- Patients who started a previous MDS related treatment less then 12 weeks ago apart from packed cell transfusions.
- Diagnosis of any previous or concomitant malignancy **except** when the patient successfully completed treatment (chemotherapy and/or surgery and/or

radiotherapy) with curative intent for this malignancy at least 3 months prior to inclusion.

- Patients refusing to sign informed consent

8 Treatment scenarios

Possible different scenarios and what to do when any of those scenarios occur, are outlined in the flowchart 'Treatment scenarios'.

8.1 Standard study visits

The patient will fill out the QUALMS and B-IPQ at timepoints 0 (at timepoint new diagnosis or timepoint new therapy), at 4 weeks, at 12 weeks and at 24 weeks on treatment. The treating physician will fill out the corresponding CRF at each timepoint. Beyond 24 weeks, no follow-up is needed.

8.2 Treatment under investigation is stopped

In case the patient stops the previously started treatment that is currently under investigation before the evaluation at 24 weeks is done, an end of treatment evaluation and follow-up needs to be performed as outlined in the section beneath 'follow-up'.

8.3 A new treatment is added less then 4 weeks after starting the investigational treatment

In case another therapy is added within 4 weeks of a previously started treatment, the patient drops out of the study. This needs to be reported to the coordinating center. No further follow-up is needed. The patient can be included in this study in the future in case the in- and exclusion criteria are met.

8.4 A new treatment is added between the timepoint of 4 and 12 weeks

If the previous treatment under investigation is transfusion of packed cells, the patient can continue to participate in this study and will restart at time point 0. The patient will cross over to the other treatment cohort. Further timepoints will be as outlined previously with completion of the questionnaires at 4, 12 and 24 weeks after the start of this new therapy.
In case the previous treatment is any other therapy than transfusion of packed cells the patient will drop out of the study. This needs to be reported to the coordinating center. No further follow-up is needed.

8.5 A new treatment is added after the timepoint of 12 weeks

The patient can continue to participate in this study. The patient will cross over to the other treatment cohort and restart at time point 0. Further timepoints are at 4,12 and 24 weeks in this new treatment as mentioned earlier.

8.6 Treatment is stopped and another treatment is started

If the patient stops the treatment that is under investigation and starts a new therapy immediately, an end of treatment evaluation is performed. This end of treatment evaluation is then used as the first time-point. Further timepoints are at 4,12 and 24 weeks after starting the new treatment.

8.7 The patient proceeds to allogeneic stem cell transplantation

In case of proceeding to allogeneic stem cell transplantation this needs to be reported. An end of treatment evaluation is done before the start of conditioning therapy. After this, the study will stop for this patient. No further follow-up is needed.

8.8 The patient progresses to acute leukemia

In case the patient progresses to acute leukemia an end of treatment evaluation is performed after the patient is aware of the diagnosis. A follow-up is performed afterwards, as described below.

8.9 The patient develops another malignant disease

In case the patient develops a new malignancy (apart from non-invasive skin cancers) that requires treatment during the treatment currently under investigation, an end of treatment evaluation will be performed and the patient will drop out of this study.

8.10 The patient dies during the study period

In case the patient dies during the study, the cause of death needs to be reported to the coordinating center.

8.11 End of treatment

An end of treatment evaluation implies filling out the QUALMS and B-IPQ by the patient at time treatment is stopped before the timepoint at 24 weeks. This implies that data will be missing at one or more forseen timepoints. At this moment, the end of treatment CRF form is completed by the treating physician. The patient will drop out of the study.

8.12 Follow-up

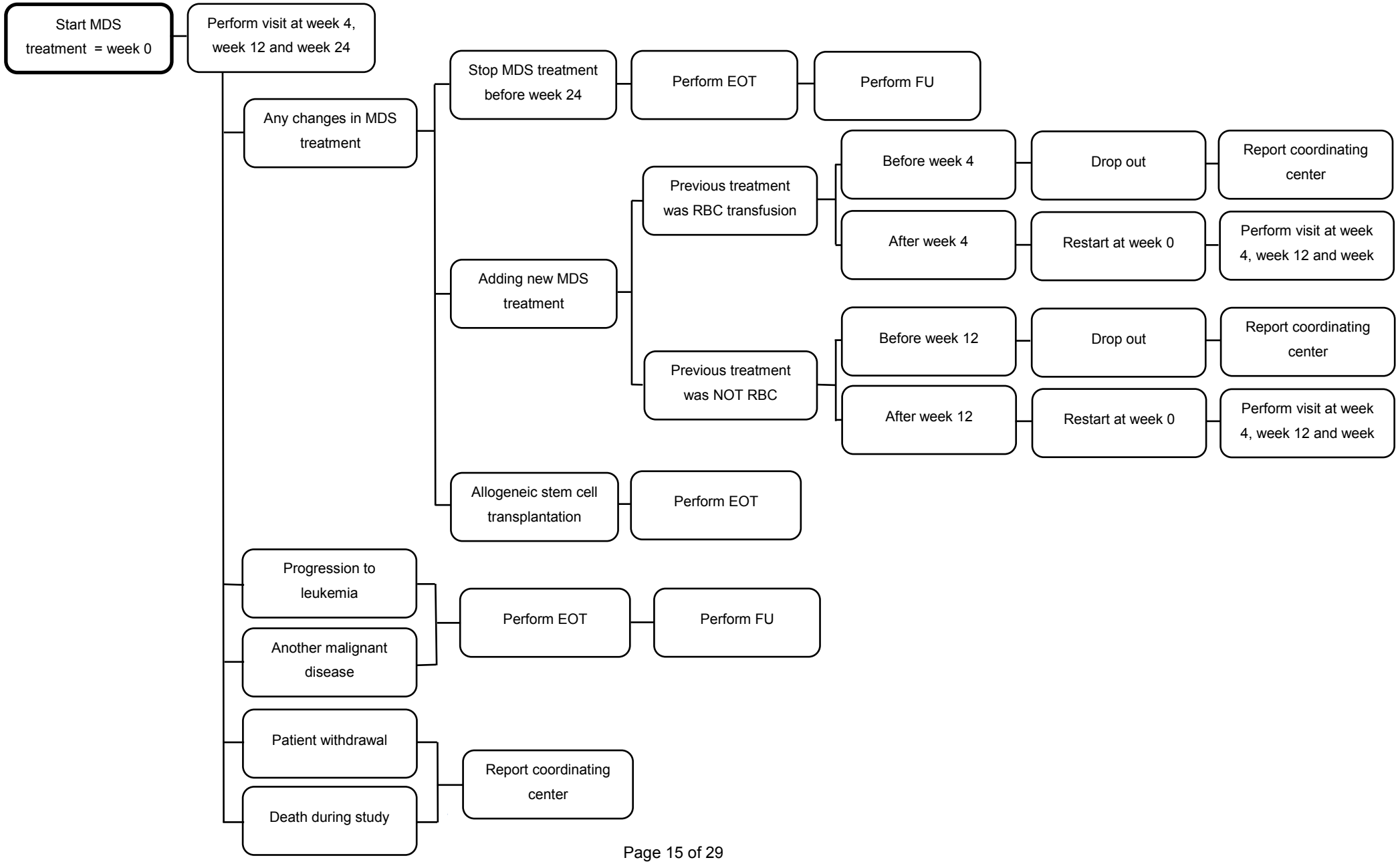
A follow up is needed after end of treatment, apart from patients that proceed to allogeneic stem cell transplantation or patients that are restart with emediatly with another therapy. The QUALMS and B-IPQ are filled out by the patient at the follow-up time point, 4 weeks after end of treatment. The phycisian will fill out the follow-up CRF form. In case the patient starts a new treatment before the follow-up time point, the patient can be included again in this new treatment group at timepoint 0.

8.13 Sequential inclusion of the same patient

In case the patient meets inclusion and exclusion criteria at a later stage, participation is allowed after filling out the application form. The same unique patient code will always be used for the same patient,

even when he drops out of the study and is included again afterwards. When included again the patient will always start at timepoint 0.

Figure 1: Flowchart Treatment Scenarios



9 Treatments studied

As mentioned before, treatment options in regard to MDS are limited for the moment. In this study, we aim to evaluate 7 treatment groups. Patients included in an interventional trial with a treatment not included in one of the 7 groups can be included but will not be part of the statistical analyses. However, the data of those patients will be reported. Specific side effects of the different treatments need to be reported as mentioned in the study safety paragraph. The different treatment groups are:

9.1 Packed cells transfusions without other treatments.

This group contains patients receiving packed cell transfusions at a rate that is determined by the treating hematologist and at a hemoglobin threshold or with a hemoglobin goal determined by the treating hematologist. In this group only patients will be evaluated who did not receive any transfusions in the past in regard to their diagnosis of MDS. The first QUALMS can be filled out during the first transfusion. In case transfusion is urgent, the first QUALMS can be filled out until 2 weeks after the first transfusion. In this case the patient must be asked to fill out the questionnaires as he was before the first transfusion. Beyond two weeks of the first transfusion we do not consider the patient to be able to recall their situation precise enough to fill out the questionnaires in retrospect. When the questionnaires are filled out in retrospect, the date of first transfusion will be taken as time point 0. The next measuring point is 4 weeks after the first transfusion as mentioned earlier. Since transfusion instantly contributes to a better hemoglobin value, we expect to measure an immediate impact on QOL.

9.2 Erythropoietin stimulating agents

Erythropoietin stimulating agents (ESA) are used frequently in low risk MDS patients. Different pharmaceutical companies provide ESA in medical need programs. This study will not differentiate between darbepoietin alfa or epoietin alfa/beta. We will not interfere with medical need programs. Obtaining and administering this medication remains the full responsibility of the treating hematologist as this study is observational only.

9.3 Deferoxamine (Desferal®)

This is a frequently used iron chelator. Administration is possible via different routes apart from oral administration. No difference will be made depending on the route or dose that is used for administration of the medication.

9.4 Deferasirox (Exjade®)

Desferasirox is an oral iron chelator. The formula was changed recently with a positive impact on tolerance of this medication (9). This study will not differentiate between different doses of the medication that are used.

9.5 5'azacytidine (Vidaza®)

5'azacytidine is an old molecule that was first developed in the sixties. Renewed interest resulted from its role as a de novo methyl transferase (DNMT) inhibitor. Registered as Vidaza®, 5'azacytidine became one of the few options available for non-transplant eligible patients suffering from myelodysplastic syndromes. Administration is subcutaneous during 7 consecutive days every 28 days or in a 5+2 regimen with a pause during the weekend. Some physicians extend treatment cycles beyond the recommended 4 weeks (28 days). This adaptation is the responsibility of the treating hematologist and must not be reported. Median time to response is 4 to 6 cycles.

9.6 Lenalidomide (Revlimid®)

Revlimid is only reimbursed in patients suffering from low risk transfusion dependent MDS with a unique deletion in the long arm of chromosome 5 (del(5q)). Since this is a rare entity with an incidence of about 20 per year in Belgium, we hope to include as much patients as possible. This medication is also used as 'ad-on' in clinical studies. Patients starting with lenalidomide together with another MDS treatment are excluded from the study as stated in the exclusion criteria (Patients starting multiple treatments at the same moment are excluded).

9.7 Intensive chemotherapy

This therapy is frequently used to reduce disease burden in anticipation to allogeneic stem cell transplantation. Without stem cell transplantation, a durable remission can be obtained but will bring no cure. Different regimens can be used. Intensive chemotherapy is considered to be high dose chemotherapy that is administrated intravenously in the hospitalized patient resulting in a prolonged period of neutropenia. No difference will be made between different regimens that are used. Since this treatment comes with his own peculiar physical and psychological impact other treatments may be started at the same moment. If the patient is treated with intensive chemotherapy he will be evaluated in the intensive chemotherapy-group only from the moment he starts this treatment.

10 Study procedures

Patients will be asked to fill out the QUALMS and the B-IPQ before starting treatment or before the start of a new therapy. The first visit, patients fill out the QUALMS and B-IPQ will be between 2 weeks before starting this therapy and the actual moment of their new treatment.
Repeated testing using the QUALMS and B-IPQ will be done 4, 12 and 24 weeks after the actual start of therapy. The treating hematologist will be asked to fill out a case report form (CRF), every time the QUALMS and B-IPQ are filled out by the patient. All questionnaires must be filled out on site only. It is not allowed to take the questionnaires home. The first QUALMS and B-IPQ must be filled out in the ambulatory setting.

10.1.1 Quality of Life

QOL will be assessed by using of the QUALMS:

The QUALMS is a disease specific questionnaire for patients suffering from a myelodysplastic syndrome. This questionnaire was developed by Abel and colleagues at the Danna-Farber institute and has been validated in an international study (1). The Dana-Farber institute, who holds editorial rights, cannot be held responsible in any way for any damage, physical or psychological that resulted from the use of their questionnaire. The data collected by the use of this questionnaire will be intellectual property of the sponsor.

10.1.2 Ilness perception

Ilness perception will be assessed by means of the B-IPQ:
Ilness perception is the idea a patient has about his or her disease and the meaning that is given to that particular idea. This perception can change during the coarse of a treatment. Since this perception may have an impact on the psychological well being of a patient, it is not unlikely that this will influence the patients` quality of life. To measure this perception, a validated questionnaire is used in his brief form, the B-IPQ (Brief illness perception questionnaire) (2).

11 Withdrawal of patients or premature termination of the study

11.1 Withdrawal of individual patients from protocol treatment

Patients should be withdrawn from protocol if any of the following criteria for withdrawal are met:

- Death
- Patient receiving different treatments within a timespan that is not allowed according to this protocol as mentioned earlier
- Patients developing another malignancy
- Patients progressing to acute leukemia
- Patients proceeding to allogeneic stem cell transplantation

Patients are allowed to withdraw from the study at any time for any reason if they wish to do so without any consequences. The investigator can also decide to withdraw a patient from protocol for other reasons than the criteria described above.

12 Safety

12.1 Reporting of adverse events.

An adverse event (AE) is any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. In contrast, an adverse reaction is characterized by the causal relationship between a medicinal product and any negative occurrence. The Belgian law recommends all physicians to report adverse reactions to the federal agency for medicines and health products (famhp) by use of the yellow paper or online.
Due to the purely non-interventional nature of this study, reporting to the sponsor should be done as per legislation for spontaneous reporting. In case an adverse reaction occurs, a parallel reporting to the famph and to the coordinating centre of this study must be performed. The coordinating centre (sponsor) will forward this report to Celgene. A general understanding to any occurred adverse events in the preceding period will come forward in the CRF that will be filled out during follow-up as outlined previously.
In case pregnancy occurs during study while the patient is taking an 'imid' drug, the drug must be stopped immediately and reporting should be done by the local investigator in accordance with the obligatory pregnancy prevention program (PPP) before prescribing an 'imid' drug.

12.2 Study Report

If the Regulations require that the Sponsor or the Principal Investigator submits a report to the competent authority or ethics committee about the Study upon completion or premature-termination of the study. The sponsor of the study shall provide a copy of that report to Celgene.

If the Regulations do not impose that obligation upon the Sponsor or the Principal Investigator, the Sponsor shall prepare a report regarding the Study. The Study report shall contain a presentation of the study objectives, the study design, the statistical methods and the outcome of the analysis of the data collected for the purpose of the Study. The Sponsor shall provide a copy of that report to Celgene.

13 Endpoints

13.1 Primary endpoint

Change in QUALMS score at timepoint 4 – 12 – 24 weeks after the start of a new treatment.

13.2 Secondary endpoints

- Change in B-IPS score at timepoint 4 – 12 – 24 weeks after the start of a new treatment
- Association between B-IPQ and QUALMS score.
- Association between clinical and disease specific factors and QUALMS score
- Association between transfusion threshold and QUALMS score.

- Association between hematological response and QUALMS score

14 Statistical considerations

14.1 Patient numbers and power considerations

The study will include 50 patients per treatment of interest. Assessing the change in QOL for seven different treatments hence results in a final sample size of 350.

14.2 Statistical analysis

At 5% significance level and 80% power, the proposed study needs to include 50 patients per group (with a group being a treatment of interest) in order to be able to detect a difference of 7.5 points in the QOL score. We hereby assume that the quality of life, as assessed by the QUALMS questionnaire, has a standard deviation of 15 points in all groups. This estimate was taken from the QUALMS validation study who assessed QOL using the QUALMS questionnaire in 255 MDS patients living in the US, Canada or Italy.

Treating the QOL as a normally distributed parameter, we computed sample size based on paired t-tests comparing the QOL at the follow-up time-points with the QOL at the start of the study, resulting in three pairwise comparisons of the following form:

$H_0: \mu_i = \mu_j$

$H_A: \mu_i \neq \mu_j$

with *i* = (0, 0, 0) and *j*= (4, 12, 24)

Because multiple comparisons are made using the same data, the significance level for sample size calculations was adjusted using a Bonferroni correction to 0.016, which results in a sample size (per treatment group) of 45.20.

Accounting for the possibility of patients to drop out of the study, this sample size is increased with 10%, resulting in a sample size (per treatment group) of 49.72, and hence a need to include 50 patients for each treatment of interest.

During an interim analysis (after approximately 4 months), we will assess the sample size needed to detect a difference of 7.5 points, based on an estimate for the standard deviation in the specific study populations, and the sample size will be adjusted accordingly.

14.3 Statistical analysis

The differences in QOL will be studied by means of a linear mixed model with time as categorical covariate. By including a random intercept per patient, we account for the correlation arising from repeatedly measuring the same patients. Post-hoc comparisons will be made to compare the QOL after 4, 12 and 24 weeks with the baseline measurements.

Similarly a linear mixed effects model will be used to examine the differences in disease perception. The impact of disease perception on QOL will be assessed by a linear mixed model with QOL as outcome, disease perception as covariate and a random intercept per patient. In the same way, the relationship between QOL and clinical and disease specific factors will be studied.
More details on the statistical procedures can be found in the statistical analysis plan.
Analyses will be performed by a certified statistician, using statistical software programs R and SAS. A significance level of 0.05 will be maintained and all estimates will be accompanied by 95% confidence intervals.

15 Trial conduct and Registration

15.1 Trial conduct

This observational, non-interventional, multi-center study will be conducted in different centers where MDS patients are treated and followed by certified hematologists. The incidence of myelodysplasia in Belgium is around 500/year with around 130 higher risk patients starting with Vidaza® annually. The prevalence however is higher since life expectancy is relatively good, especially in lower risk patients. The target to include differs in respective to the started therapy. Our inclusion goal is a minimum of 50 patients per treatment. In the specific situation of MDS with isolated del(5q) we aim to include as much patients as possible. The total inclusion goal is 350 patients.
The coordinator of the study is the department of hematology, Universitair ziekenhuis Antwerpen in close collaboration with Ziekenhuis Netwerk Antwerpen. A PowerPoint presentation will be made as a study initiation tool. No one from the coordinating center will visit the participating centers in regard to this study. Questions can be directed to any of the contact persons of the coordinating centers.

All questionnaires and report forms will be provided by the coordinating center.
Storage of the signed ICF and data collection will take place locally. A copy or scan of the filled-out questionnaires is stored locally, the original questionnaires and CRF's must be send to the data management team of ZNA. Data entry and processing will be done by the data management team of ZNA under supervision of the study coordinators.

15.2 Regulatory Documentation

Required regulatory and administrative documents must be provided to the ZNA before enrolment of the first patient. This will always include an Ethics Committee approval for the investigational site. The ZNA will provide each investigator with an overview of the required documents. Each investigational site will be notified when all requirements are met and enrolment can start.

15.3 Registration

Eligible patients should be registered before start of treatment. Patients need to be registered by filling out the registration form and sending this by email to: **be.qualms@zna.be**

The following information will be requested at registration:

All eligibility criteria will be checked with a checklist.
Each patient will be given a unique patient study number that is provided by the coordinating center. Patient study number will be given by email.

16 Data collection and quality assurance

Handing out and collecting the questionnaires to and from the patients will be done by local data nurses. The local data center will hold a copy of the filled-out questionnaire. The original filled out questionnaires and CRF forms will be sent to the data center at ZNA. At ZNA the local data management will be responsible for the processing of the questionnaire data and CRF forms.
Input of the questionnaires in the database will be automatized in order to avoid copy mistakes. A special software is developed that can scan the questionnaires and load the data in our database that will hold all the information. Reading of the questionnaires will be done every 4 weeks at ZNA. The original filled out questionnaires will be stored at the clinical trials unit of UZA afterwards.
The CRF forms will be brought into the database manually with a double cross check. Students will be employed for this processing under supervision of one of the co-investigators.
After the data are processed they will be ready for statistical analyses. The database with the available data remains intellectual property of the principal and co-investigators, for any further use of the database the permission of all data owners is mandatory.

16.1 Data quality assurance

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the investigator before the study.
Data collected will be verified for accuracy. If necessary, queries will be sent to the investigational site to clarify the data. The investigator should answer data queries within the specified time line.

17 Ethics

17.1 Accredited ethics committee

An accredited Ethics Committee will approve the study protocol and any substantial amendment.

17.2 Ethical conduct of the study

The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki (2013, www.wma.net)), the ICH-GCP Guidelines, the EU Clinical Trial Directive (2001/20/EG), and applicable regulatory requirements. The local investigator is responsible for the proper conduct of the study at the study site.

17.3 Patient information and consent

Written informed consent of patients is required before enrolment in the trial and before any study related procedure takes place.
The investigator will follow ICH-GCP and other applicable regulations in informing the patient and obtaining consent. The investigator should take into consideration if the patient is capable of giving informed consent. Before informed consent may be obtained, the investigator should provide the patient ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial, at least one week, if medically possible. All questions about the trial should be answered to the satisfaction of the patient.
There is no set time limit for the patient to make a decision. The investigator should inform each patient if there is a specific reason why he/she must decide within a limited time frame, for example if patients condition necessitates start of treatment or if the trial is scheduled to close for enrolment.

The content of the patient information letter, informed consent form and any other written information to be provided to patients will be in compliance with ICH-GCP and other applicable regulations and should be approved by the Ethics Committee in advance of use.
The patient information letter, informed consent form and any other written information to be provided to patients will be revised whenever important new information becomes available that may be relevant to the patient's consent. Any revised informed consent form and written information should be approved by the Ethics Committee in advance of use. The patient should be informed in a timely manner if new information becomes available that might be relevant to the patient's willingness to continue participation in the trial. The communication of this information should be documented.

17.4 Trial insurance

In accordance with the Belgian law relating to experiments on human persons dated May 7, 2004, the sponsor shall assume, even without faults, the responsibility of any damages incurred by a study patient and linked directly or indirectly to the participation to the study and shall provide compensation through its insurance.

18 Administrative aspects and publication

18.1 Handling and storage of data and documents

18.1.1 Patient confidentiality

Each patient is assigned a unique patient study number at enrolment. In trial documents the patient's identity is coded by patient study number as assigned at enrolment.
The local investigator will keep a subject enrolment and identification log that contains the key to the code, i.e. a record of the personal identification data linked to each patient study number. This record is filed at the investigational site and should only be accessed by the investigator and the supporting site staff, and by representatives of the sponsor or a regulatory agency for the purpose of monitoring visits or audits and inspections.

18.1.2 Filing of essential documents

Essential Documents are those documents that permit evaluation of the conduct of a trial and the quality of the data produced. The essential documents may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory authority(ies).
The investigator should file all essential documents relevant to the conduct of the trial on site. The sponsor will file all essential documents relevant to the overall conduct of the trial. Essential documents should be filed in such a manner that they are protected from accidental loss and can be easily retrieved for review.

18.1.3 Record retention

Essential documents containing study data, including case report forms, should be retained for 20 years after the end of the trial. They should be destroyed after this time.
Source documents (i.e. medical records) of patients should be retained for at least 30 years after the end of the trial. Record retention and destruction after this time is subject to the site's guidelines regarding medical records.

18.2 End of study report

The sponsor will notify the accredited Ethics Committee and the Competent Authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the sponsor will notify the accredited Ethics Committee and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the trial, the sponsor will submit an end of study report with the results of the study, including any publications/abstracts of the study, to the accredited Ethics Committee and the Competent Authority.

18.3 Financial regulations

This academic study is financially supported by Celgene as an investigator initiated trial. A fee of 250 euro (inc VAT, inc overhead) per completed patient is foreseen to cover local logistic costs.

18.4 Publication policy

The results of this study will be published in a multi-center publication, based on the data of all participating clinical sites. Participating sites are not allowed to publish any of their data or results from the study, prior to the multicenter publication.
Any publication by a participating site will be submitted to the sponsor for review at least thirty days prior to submission or disclosure. The sponsor shall have the right to delay the projected publication for a period of up to three months from the date of first submission to the sponsor in order to enable the sponsor to take steps to protect its intellectual property rights and know-how.
Publications will be coordinated by the Principal and Co-investigators.

Authors of the main manuscript include the Principal Investigator and the Coinvestigator(s)s. Others who have made a significant contribution to the trial may also be included as author, or otherwise will be included in the acknowledgement. The Principal and co-investigators will use the maximum number of authors allowed by the journal to the full extent and the authors will be included on account of inclusion rate.

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Annex 1

The Qualms

Annex 2

The Brief Illness Perception Questionnaire